Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 878–882, February 1993
Neurobiology

Functional activation of the human frontal cortex during the performance of verbal working memory tasks

MICHAEL PETRIDES, BESSIE ALIVISATOS, ERNST MEYER, AND ALAN C. EVANS

Montreal Neurological Institute, McGill University, Montreal, Quebec H3A 2B4, Canada

Communicated by Brenda Milner, September 22, 1992

ABSTRACT **Regional cerebral blood flow was measured with positron emission tomography during the performance of verbal working memory tasks. The same type of verbal response (i.e., reciting numbers) was required in the control and the two experimental tasks. In the control task, the subjects were required to count aloud. In the two experimental tasks, the subjects were required to maintain within working memory the numbers they generated (self-ordered task) or the numbers generated by the experimenter (externally ordered task). Examination of the difference in activation between these conditions revealed strong bilateral activation within the mid-dorsolateral frontal cortex during both experimental tasks. There was, however, no evidence of additional activation within the mid-dorsolateral frontal cortex when monitoring self-generated responses as compared with the monitoring of externally generated responses. These results provide evidence regarding the role of the mid-dorsolateral frontal cortex in mnemonic processing that are in agreement with recent findings from work with non-human primates.**

Patients with lesions involving the lateral frontal cortex are impaired on certain working memory tasks that require monitoring of self-generated responses (1). Work with non-human primates demonstrated that the mid-dorsolateral frontal cortex, comprising cytoarchitectonic areas 46 and 9, is a critical region for the performance of such tasks (2, 3). In a recent investigation with positron emission tomography (PET), we examined regional cerebral blood flow (rCBF), a marker of local neuronal activity, in normal human subjects while they were carrying out a series of self-generated pointing responses to a set of abstract designs (4, 5). Significant increases in rCBF were observed within the mid-dorsolateral frontal cortex, confirming the importance of this region of the frontal cortex for this aspect of working memory, as was originally shown by the animal work. These rCBF increases were more pronounced within the right mid-dorsolateral frontal cortex, most probably reflecting the fact that the type of stimulus material (i.e., abstract designs) used in that investigation is primarily processed by the right hemisphere (6).

The purpose of the present investigation was 2-fold: (*i*) to determine whether monitoring self-generated choices within the verbal domain would also result in activation of the mid-dorsolateral frontal cortex and whether this activation would be pronounced within the left cerebral hemisphere and (*ii*) to examine whether the mid-dorsolateral frontal cortex would also be critically involved in comparable working memory tasks requiring monitoring of a set of stimuli that are externally generated. This question arose from the following observations. A recent investigation (7) has replicated our original demonstration (1) of an impairment in the monitoring of self-generated responses following damage to the human frontal cortex and it has suggested that this impairment does not extend to the monitoring of externally generated stimuli. This finding is at variance with recent experiments with non-human primates analyzing the nature of the mnemonic impairment that follows lesions confined to the mid-dorsolateral frontal cortex. These experiments have shown that such lesions impair the monitoring of self-generated responses and externally generated stimuli (M.P., unpublished data; ref. 8). On the basis of these recent findings with non-human primates, we predicted strong activation within the human mid-dorsolateral frontal cortex on a working memory task involving monitoring of a series of externally generated stimuli.

METHODS

Subjects. Ten right-handed male volunteer subjects participated in this experiment. Their ages ranged from 19 to 39 years (mean age, 24.2 years). All subjects gave informed, written consent for participation in the study after its nature and possible consequences were explained to them. The study was approved by the Ethics Committee of the Montreal Neurological Hospital.

Scanning Methods and Data Analysis. PET scans were obtained with a Scanditronix PC-2048 tomograph that produces 15 image slices at an intrinsic resolution of 5 × 5 × 6 mm (9). The regional distribution of rCBF was measured by means of the water bolus $H_2{}^{15}O$ methodology (10) during 60-sec scanning conditions. Each subject also underwent a high-resolution magnetic imaging resonance (MRI) scan (64 slices, 2 mm thick) obtained with a Philips Gyroscan (1.5 T). The MRI scans were resliced so as to be in register with the PET data, using a PIXAR three-dimensional (3D) computer (11). Interactive 3D image software was then used to establish an orthogonal coordinate frame based on the anterior–posterior commissure line as identified in the MRI image volume (12). These coordinates were used to apply a linear resampling of each matched pair of MRI and PET data sets into a standardized stereotaxic coordinate system (13). To overcome residual anatomical variability persisting after the stereotaxic standardization, the PET images were smoothed with a 20-mm Hanning filter. PET images were normalized for global rCBF and the mean state-dependent rCBF difference image volume was obtained (14). This volume was converted to a *t*-statistic volume by dividing each voxel by the mean standard deviation in normalized rCBF for all intracerebral voxels (15). Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes, 128 × 128 × 80 voxels in extent and sampled at 1.34 × 1.72 × 1.50 mm in the *x*, *y*, and *z* dimensions, respectively, were obtained for *t*-statistic and MRI volumes. Anatomical and functional images were merged (12), a procedure that allows (*i*) direct localization of *t*-statistic peaks, identified by an automatic peak-detection algorithm, on the MRI images and (*ii*) the anatomical correlation of extended zones of activation that cannot be ex-

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: PET, positron emission tomography; rCBF, regional cerebral blood flow.

Table 1. Self-ordered task minus control counting task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
				Left hemisphere
−40	32	30	4.18	Mid-dorsolateral frontal cortex (area 9)
−35	42	22	4.57	Mid-dorsolateral frontal cortex (area 46)
−20	8	62	4.10	Posterior premotor cortex
−16	12	48	5.57	Posterior premotor cortex
−11	25	22	4.96	Anterior cingulate cortex (area 24)
−1	−69	47	6.26	Posterior parietal cortex (area 7)
−35	−49	40	4.31	Posterior parietal cortex (area 40)
				Right hemisphere
38	39	26	5.09	Mid-dorsolateral frontal cortex (area 46/9)
27	5	58	5.79	Posterior premotor cortex
42	−44	49	5.35	Posterior parietal cortex (area 40)
31	−62	42	5.05	Posterior parietal cortex (area 40)

Activation foci in this and the other tables represent peaks of statistically significant (see text) increases in normalized CBF. The stereotaxic coordinates are expressed in mm. *x*, Medial-to-lateral distance relative to the midline (positive = right); *y*, anterior–posterior distance relative to the anterior commissure (positive = anterior); *z*, superior–inferior distance relative to the anterior commissure–posterior commissure line (positive = superior).

pressed in terms of isolated peaks. Mapping the subject's own MRI into stereotactic space overcomes some of the

Table 2. Externally ordered task minus control counting task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
				Left hemisphere
−35	24	31	4.89	Mid-dorsolateral frontal cortex (area 9)
−32	44	18	4.37	Mid-dorsolateral frontal cortex (area 46)
−32	5	53	5.04	Posterior premotor cortex
−38	−50	42	5.15	Posterior parietal cortex (area 40)
				Right hemisphere
27	29	36	4.32	Mid-dorsolateral frontal cortex (area 9)
40	34	29	5.15	Mid-dorsolateral frontal cortex (area 46/9)
25	58	8	4.53	Frontopolar cortex (area 10)
25	6	60	5.04	Posterior premotor cortex
3	−68	47	6.33	Posterior parietal cortex (area 7)
38	−52	45	5.15	Posterior parietal cortex (area 40)
19	−66	42	4.48	Posterior parietal cortex (area 7)
31	−64	49	5.82	Posterior parietal cortex (area 7)

difficulties associated with using a standard atlas alone to identify anatomical correlates of the PET responses in areas of high anatomical variability (12).

For an exploratory search involving all peaks within the grey matter volume of 600 cm^3, the threshold for reporting a peak as significant was set at $t = 3.50$, corresponding to an

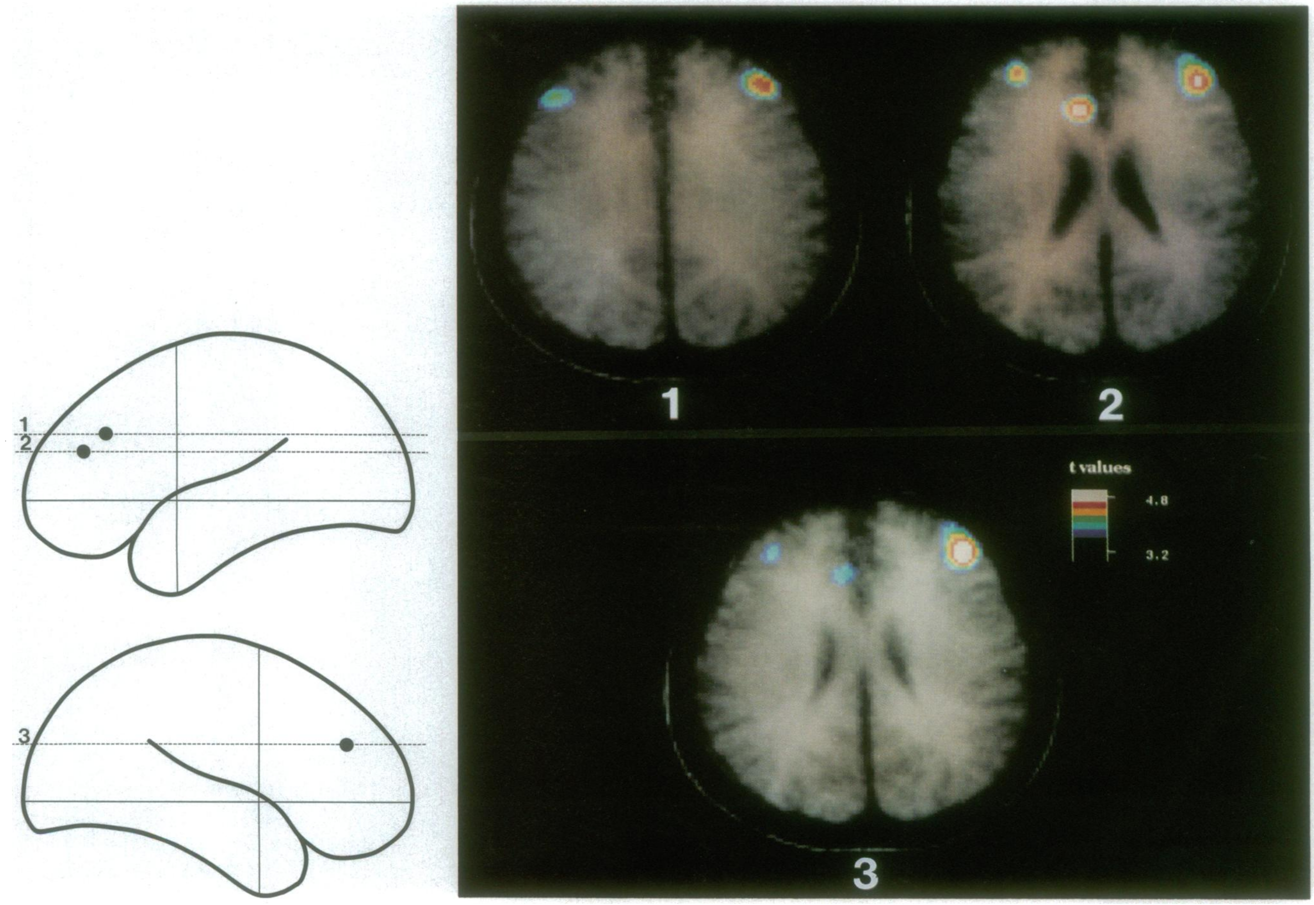

FIG. 1. Self-ordered minus control task. Merged PET-MRI horizontal sections showing activation foci within the mid-dorsolateral frontal cortex. The schematic outlines of the brain indicate the level (interrupted lines) of the sections presented. The subject's left is on the left side in these sections. The coordinates (*x*, *y*, *z*) of the foci shown on the schematic outlines of the brain are 1, 40, 32, 30; 2, 35, 42, 22; and 3, 38, 39, 26.

uncorrected probability of $P < 0.0002$ (15). A directed search within the dorsolateral frontal cortex for predicted activation foci in particular cytoarchitectonic areas was also carried out and for this analysis the threshold for significance was set at $t = 3.00$, corresponding to an uncorrected probability of $P < 0.0013$.

Testing Procedure. In this experiment, the subjects were scanned with PET for 60 sec under three different conditions of testing. In the control condition, the subjects were required to count aloud from 1 to 10 at the rate of approximately one digit per second. They were told that when they reached the number 10, they were once again to start counting from 1 to 10 and continue in this manner until told to stop. In the self-ordered condition, the subjects were asked to say aloud, in a random order, the numbers from 1 to 10. They were asked to monitor carefully the numbers they gave so as not to repeat the same number more than once until all 10 numbers were reported. At that point they were to begin a new trial (i.e., a sequence), again generating numbers randomly from 1 to 10. The subjects were asked to start always from the number 1, because this would permit the experimenter, who was recording the responses, to know when a new trial had begun. As in the control condition, the subjects were told to generate the numbers at the rate of approximately one per second. An average of 5.25 trials (range, 4.5–6.0) was completed during scanning, with an average error of 0.9. An error was defined as a repetition or an omission of a number in a trial. In the externally ordered condition, the subjects were told that, during scanning, the experimenter would read out in a random sequence the numbers from 1 to 10, omitting one of these numbers. The subjects had to monitor carefully the numbers read by the experimenter because, on completion, they would have to say the number that had been omitted. The experimenter would then administer another trial—i.e., read another random sequence of the numbers 1 to 10, again omitting one number that the subject would be required to report. The numbers were read out at the rate of approximately one digit per second. An average of 5.6 (range, 5.0–6.0) trials was completed during scanning and the subjects made an average error of 0.2 per trial.

Before each scanning condition, the experimenter explained the requirements of the task to be performed and the subjects practiced the task once. The subjects kept their eyes open during scanning, but visual stimulation was reduced by dimming the lights within the scanning room and by surrounding the subject with black curtains.

RESULTS

In the two experimental tasks, the subjects were required to maintain within working memory the numbers they generated (self-ordered task) or the numbers generated by the experimenter (externally ordered task). Subtractions of activation between different conditions were employed to observe rCBF changes in a given condition with reference to activation in another condition. The significant foci of rCBF changes resulting from subtraction of activation in the control condition from activation in the self-ordered condition and the externally ordered condition are presented in Tables 1 and 2, respectively, which show that there was strong activation within the mid-dorsolateral frontal cortex (see also Figs. 1 and 2) related to the performance of the self-ordered and the externally ordered working memory tasks.

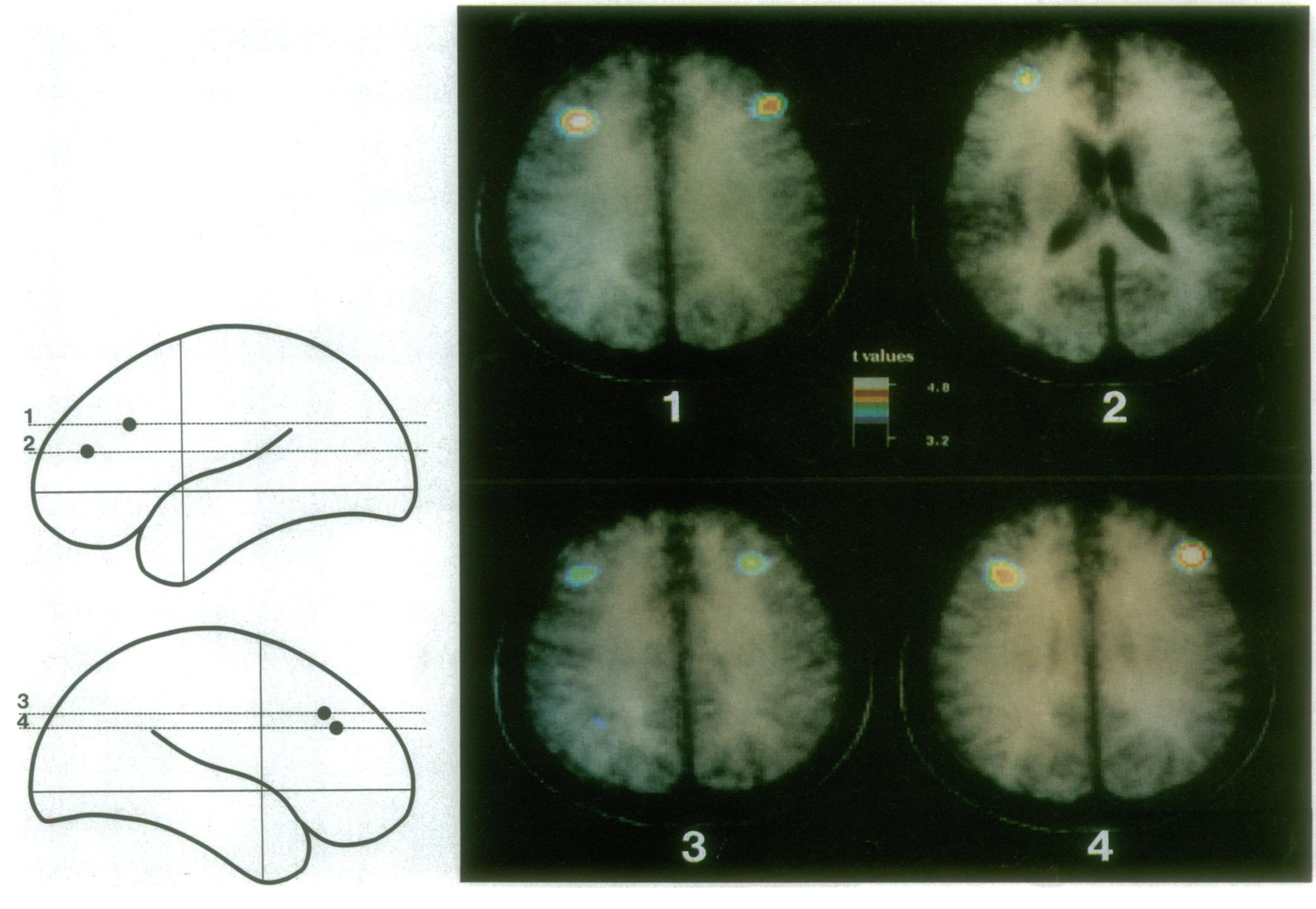

FIG. 2. Externally ordered minus control task. Merged PET-MRI horizontal sections showing activation foci within the mid-dorsolateral frontal cortex. The coordinates (*x, y, z*) of the foci shown on the outlines of the brain are 1, 35, 24, 31; 2, 32, 44, 18; 3, 27, 29, 36; and 4, 40, 34, 29.

Table 3. Difference between self-ordered task minus externally ordered task and externally ordered task minus self-ordered task

Stereotaxic coordinate				
x	*y*	*z*	*t* statistic	Brain area
Self-ordered task minus externally ordered task				
				Midline
0	3	65	5.89	Supplementary motor area
				Left hemisphere
−50	−11	38	5.12	Motor cortex (face area)
−17	−59	−17	4.86	Cerebellum
−43	12	9	3.96	Broca's area (area 44)
				Right hemisphere
44	−6	36	4.90	Motor cortex (face area)
59	−1	21	3.62	Motor cortex (face area)
8	−66	−12	4.05	Cerebellum
1	−37	−8	3.92	Brainstem
Externally ordered task minus self-ordered task				
				Left hemisphere
−59	−26	−2	4.08	Lateral temporal cortex (area 21)
−55	−30	8	4.12	Lateral temporal cortex (area 22)
−35	−28	−18	3.91	Ventral temporal cortex (area 20/36)
				Right hemisphere
52	−28	−6	4.89	Lateral temporal cortex (area 21)
42	−62	21	3.91	Posterior lateral temporal cortex

A second question of interest in the present investigation was whether there would be activation within the mid-dorsolateral frontal cortex specifically related to the self-generation of responses or the monitoring of externally generated responses when the mnemonic requirements were controlled. To address this question, we subtracted activation between the self-ordered task and the externally ordered task. The results of this subtraction are shown in Table 3. The self-ordered task resulted in activation in regions of the brain that are known to be involved in various aspects of language production (see Table 3 and Fig. 3), whereas the externally ordered task activated regions of the brain that are involved with the receptive aspects of language (see Table 3).

A major difference between the self-ordered and the externally ordered task in terms of activation within the prefrontal cortex was the significant peak within the frontopolar cortex (area 10) in the externally ordered minus control subtraction (see Table 2). In the externally ordered minus self-ordered subtraction, there was also a similar activation peak within area 10 (stereotactic coordinates: $x = 20$, $y = 55$, $z = 8$) that had a t-statistic value of 3.05, which missed the threshold for significance.

DISCUSSION

The present investigation examined rCBF changes related to the performance of two working memory tasks. In the self-ordered task, the subjects had to monitor a series of self-generated verbal responses, and in the externally ordered task, they had to monitor verbal stimuli presented by the experimenter. The major issue addressed in this investigation was whether there would be activation within the mid-dorsolateral frontal cortex—i.e., cytoarchitectonic areas 46 and 9—when the subjects were performing the self-ordered task and the externally ordered task. When activation in the control condition was subtracted from either of the two experimental tasks, rCBF increases were observed bilaterally within the mid-dorsolateral frontal cortex (cytoarchitectonic areas 46 and 9). Thus, clear activation of the mid-dorsolateral frontal cortex was observed during the performance of a task requiring monitoring of self-generated responses and a task requiring externally generated responses. This conclusion was further strengthened by the fact that, when activation in the externally ordered task and the self-ordered task were subtracted from each other, no rCBF changes were observed within the mid-dorsolateral frontal cortex (see Table 3). The most intriguing difference in activation between these two tasks was the increase in rCBF of the frontopolar cortex (area 10) (Table 2) in the externally ordered task. In the latter task, the subjects had to monitor carefully the auditory input generated by the experimenter. In this respect, it is important to note that area 10 is strongly connected with auditory cortical areas of the superior temporal cortex (16, 17) and it may be involved in mnemonic processing involving auditory input.

In an earlier study with PET, we observed greater activation within the right mid-dorsolateral frontal cortex in relation to the performance of a task requiring the monitoring of self-generated choices from a set of abstract designs (4, 5). This finding was consistent with a considerable amount of evidence demonstrating that such stimulus material is preferentially processed within the right hemisphere (6). In the present investigation in which verbal material was utilized, there was strong activation within the left and the right mid-dorsolateral frontal cortex (see Figs. 1 and 2).

Activation of an extensive region of the lateral frontal cortex that included area 46 was recently reported in a PET investigation by Frith *et al.* (18) in which subjects were generating, during scanning, words beginning with a particular letter, as well as during the performance of a task requiring movement of the two fingers in a random sequence. This activation was interpreted as evidence that area 46 is specifically associated with willed actions (18). In the study

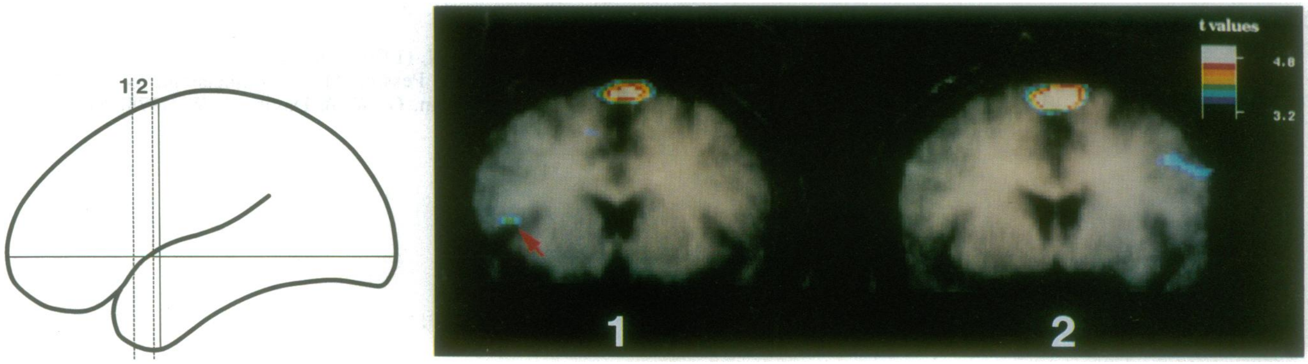

FIG. 3. Self-ordered minus externally ordered task. Merged PET-MRI coronal section 1 at 12 mm and section 2 at 3 mm to show activation of Broca's area (indicated by the arrow in section 1) and the supplementary motor area.

reported here, we examined activation in relation to two tasks that had the same requirements in terms of monitoring within working memory but differed in that one of the tasks involved self-generated (i.e., willed) responses and the other did not. As pointed out above, both tasks activated the mid-dorsolateral frontal cortex and subtraction of activation in the externally ordered task from activation in the self-ordered task did not reveal rCBF changes in the mid-dorsolateral frontal cortex specifically related to self-generation. This finding indicates that response generation was not the critical factor determining activation of area 46 but, rather, the requirement to monitor within working memory. In the study by Frith *et al.* (18), the tasks requiring the generation of words and the production of random finger movements involve, among other cognitive requirements, monitoring within working memory and, we suggest, this factor may have been the reason for the activation of area 46.

In the present investigation, subtraction of activation between the two experimental tasks yielded interesting observations with regard to cerebral regions participating in the expressive and receptive aspects of linguistic processing. When activation in the externally ordered task was subtracted from activation in the self-ordered task that emphasized verbal output, CBF increases were only observed in regions of the brain that are known to be involved in various aspects of language production (see Table 3). Conversely, subtraction of activation in the self-ordered task from that in the externally ordered task revealed CBF increases in regions of the cerebral cortex underlying receptive aspects of linguistic processing (see Table 3).

Activation of the region of the motor cortex representing the orofacial musculature, the supplementary motor cortex, and the cerebellum was previously reported in PET studies of reading aloud visually presented words or repeating auditorily presented words (19, 20). It is interesting to note that in those studies activation was also observed within the opercular cortex near, but not within, the traditionally defined Broca's area (i.e., cytoarchitectonic area 44). Since these opercular foci were also activated by simple movements of the mouth and tongue, it has been suggested that their involvement may be related to motor programing rather than specifically to linguistic function (20). Steinmetz and Seitz (21) have drawn attention to this apparent failure to activate Broca's area in the above PET studies and have raised the possibility that methodological difficulties due to intersubject averaging may account for this apparent failure. Although these factors can hinder the accurate assignment of foci near the margins of the classical Broca's area, the present study yielded a clear activation within the pars opercularis (area 44), a region considered to constitute the larger part of Broca's area. It is possible that Broca's area may not necessarily be activated in all speech production tasks, as held by the classical neurological view of brain organization for language (22). In fact, there is considerable debate concerning the precise involvement of Broca's area in linguistic processing (23). The present findings suggest that under certain conditions involving speech production this area can be activated in PET studies and that such studies hold the promise of identifying the conditions under which Broca's area and other related areas are activated, thus beginning to reveal their specific contribution to language production.

In conclusion, the present study demonstrated by means of PET the critical involvement of the mid-dorsolateral frontal cortex—i.e., areas 46 and 9—in working memory. No evidence of a specific contribution of these areas to the self-generation of responses, in contradistinction to their involvement in working memory, was provided by the present study. The monitoring within working memory of responses provided through the auditory modality engaged in addition the frontopolar cortex (area 10), a region of the frontal lobe that is heavily interconnected with auditory cortex along the superior temporal gyrus.

We thank the staff of the McConnell Brain Imaging Center for their technical assistance. This work was supported by the McDonnell-Pew Program in Cognitive Neuroscience and Medical Research Council (Canada) Special Project Grant SP-30 (coordinator: Dr. A. Gjedde). Color reproductions were supported by G. E. Medical Services.

1. Petrides, M. & Milner, B. (1982) *Neuropsychologia* **20**, 249–262.
2. Petrides, M. (1988) *Soc. Neurosci. Abstr.* **14**, 2.
3. Petrides, M. (1991) *Proc. R. Soc. London B* **246**, 293–298.
4. Petrides, M., Alivisatos, B., Evans, A. C. & Meyer, E. (1991) *Soc. Neurosci. Abstr.* **17**, 135.
5. Petrides, M., Alivisatos, B., Evans, A. C. & Meyer, E. (1993) *Proc Natl. Acad. Sci. USA* **90**, 873–877.
6. Milner, B. (1971) *Br. Med. Bull.* **27**, 272–277.
7. Wiegersma, S., van der Scheer, E. & Hijman, R. (1990) *Neuropsychologia* **28**, 95–98.
8. Petrides, M. (1991) *Proc. R. Soc. London B* **246**, 299–306.
9. Evans, A. C., Thompson, C. J., Marrett, S., Meyer, E. & Mazza, M. (1991) *IEEE Trans. Med. Imaging* **10**, 90–98.
10. Raichle, M. E., Martin, W. R. W., Herscovitch, P., Mintun, M. A. & Markham, J. (1983) *J. Nucl. Med.* **24**, 790–798.
11. Evans, A. C., Marrett, S., Torrescorzo, J., Ku, S. & Collins, L. (1991) *J. Cereb. Blood Flow Metab.* **11**, A69–A78.
12. Evans, A. C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., Milot, S., Meyer, E. & Bub, D. (1992) *NeuroImage* **1**, 43–53.
13. Talairach, J. & Tournoux, P. (1988) *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, New York).
14. Fox, P. T., Perlmutter, J. S. & Raichle, M. E. (1985) *J. Comput. Assist. Tomogr.* **9**, 141–153.
15. Worsley, K. J., Evans, A. C., Marrett, S. & Neelin, P. (1992) *J. Cereb. Blood Flow Metab.* **12**, 900–918.
16. Petrides, M. & Pandya, D. N. (1984) *J. Comp. Neurol.* **273**, 52–66.
17. Barbas, H. & Mesulam, M.-M. (1985) *Neuroscience* **15**, 619–637.
18. Frith, C. D., Friston, K., Liddle, P. F. & Frackowiak, R. S. J. (1991) *Proc. R. Soc. London B* **244**, 241–246.
19. Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M. & Raichle, M. E. (1988) *Nature (London)* **331**, 585–589.
20. Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M. & Raichle, M. E. (1989) *J. Cogn. Neurosci.* **1**, 153–170.
21. Steinmetz, H. & Seitz, R. J. (1991) *Neuropsychologia* **29**, 1149–1161.
22. Geschwind, N. (1970) *Science* **170**, 940–944.
23. Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W. & Davis, K. R. (1978) *Neurology* **28**, 311–324.